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Hyzaar—Cont.

tients with a history of hepatic impairment (see WARNINGS, *Impaired Hepatic Function*). Losartan can be administered once or twice daily at total daily doses of 25 to 100 mg. If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response.

Hydrochlorothiazide is effective in doses of 12.5 to 50 mg once daily and can be given at doses of 12.5 to 25 mg as HYZAAR.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

The side effects (see WARNINGS) of losartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of losartan and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

Replacement Therapy: The combination may be subtituted for the titrated components.

Dose Titration by Clinical Effect: A patient whose blood pressure is not adequately controlled with losartan monotherapy (see above) may be switched to HYZAAR 50-12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased to two tablets of HYZAAR 50-12.5 once daily or one tablet of HYZAAR 100-25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily.

A patient whose blood pressure is inadequately controlled by 25 mg once daily of hydrochlorothiazide, or is controlled but who experiences hypokalemia with this regimen, may be switched to HYZAAR 50-12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response. The clinical response to HYZAAR 50-12.5 should be subsequently evaluated and if blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased to two tablets of HYZAAR 50-12.5 once daily or one tablet of HYZAAR 100-25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily.

The usual dose of HYZAAR is one tablet of HYZAAR 50-12.5 once daily. More than two tablets of HYZAAR 50-12.5 once daily or more than one tablet of HYZAAR 100-25 once daily is not recommended. The maximal antihypertensive effect is attained about 3 weeks after initiation of therapy.

Use in Patients with Renal Impairment: The usual regimens of therapy with HYZAAR may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so HYZAAR is not recommended.

Patients with Hepatic Impairment: HYZAAR is not recommended for titration in patients with hepatic impairment (see WARNINGS, *Impaired Hepatic Function*) because the appropriate 25 mg starting dose of losartan cannot be given. HYZAAR may be administered with other antihypertensive agents.

HYZAAR may be administered with or without food.

HOW SUPPLIED

No. 3502—Tablets HYZAAR, 50-12.5 are yellow, teardrop shaped, film-coated tablets, coded MRK 717 on one side and HYZAAR on the other. Each tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. They are supplied as follows:

NDC 0006-0717-31 unit of use bottles of 30
NDC 0006-0717-54 unit of use bottles of 90
NDC 0006-0717-58 unit of use bottles of 100.
NDC 0006-0717-28 unit dose packages of 100
NDC 0006-0717-82 unit of use bottles of 1,000.

Shown in Product Identification Guide, page 323

No. 3793—Tablets HYZAAR 100-25 are light yellow, teardrop shaped, film-coated tablets, coded MRK 747 on one side and HYZAAR on the other. Each tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide. They are supplied as follows:

NDC 0006-0747-31 unit of use bottles of 30
NDC 0006-0747-58 unit of use bottles of 100
NDC 0006-0747-28 unit dose packages of 100.

Shown in Product Identification Guide, page 323

Storage

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.

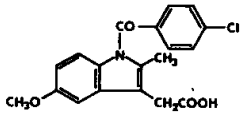
Manufactured for:
MERCK & CO., INC., West Point, PA 19486, USA
by:
DuPont Pharma, Wilmington, DE 19880 USA
7892813 Issued December 1999

INDOCIN® Capsules, Oral Suspension and Suppositories
(Indomethacin) Rx

DESCRIPTION

INDOCIN* (Indomethacin) cannot be considered a simple analgesic and should not be used in conditions other than those recommended under INDICATIONS.

INDOCIN is supplied in three dosage forms. Capsules INDOCIN for oral administration contain either 25 mg or 50 mg of indomethacin and the following inactive ingredients: colloidal silicon dioxide, FD & C Blue 1, FD & C Red 3, gelatin, lactose, lecithin, magnesium stearate, and titanium dioxide. Suspension INDOCIN for oral use contains 25 mg of indomethacin per 5 mL, alcohol 1%, and sorbic acid 0.1% added as a preservative and the following inactive ingredients: antifoam AF emulsion, flavors, purified water, sodium hydroxide or hydrochloric acid to adjust pH, sorbitol solution, tragacanth. Suppositories INDOCIN for rectal use contain 50 mg of indomethacin and the following inactive ingredients: butylated hydroxyanisole, butylated hydroxytoluene, edetic acid, glycerin, polyethylene glycol 3350, polyethylene glycol 8000 and sodium chloride. Indomethacin is a non-steroidal anti-inflammatory indole derivative designated chemically as 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid. Indomethacin is practically insoluble in water and sparingly soluble in alcohol. It has a pKa of 4.5 and is stable in neutral or slightly acidic media and decomposes in strong alkali. The suspension has a pH of 4.0–5.0. The structural formula is:



*Registered trademark of MERCK & CO., Inc.

CLINICAL PHARMACOLOGY

INDOCIN is a non-steroidal drug with anti-inflammatory, antipyretic and analgesic properties. Its mode of action, like that of other anti-inflammatory drugs, is not known. However, its therapeutic action is not due to pituitary-adrenal stimulation.

INDOCIN is a potent inhibitor of prostaglandin synthesis *in vitro*. Concentrations are reached during therapy which have been demonstrated to have an effect *in vivo* as well. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Moreover, prostaglandins are known to be among the mediators of inflammation. Since indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

INDOCIN has been shown to be an effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.

INDOCIN affords relief of symptoms; it does not alter the progressive course of the underlying disease.

INDOCIN suppresses inflammation in rheumatoid arthritis as demonstrated by relief of pain, and reduction of fever, swelling and tenderness. Improvement in patients treated with INDOCIN for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, average number of joints involved, and morning stiffness; by increased mobility as demonstrated by a decrease in walking time; and by improved functional capability as demonstrated by an increase in grip strength.

Indomethacin has been reported to diminish basal and CO_2 stimulated cerebral blood flow in healthy volunteers following acute oral and intravenous administration. In one study after one week of treatment with orally administered indomethacin, this effect on basal cerebral blood flow had disappeared. The clinical significance of this effect has not been established.

Capsules INDOCIN have been found effective in relieving the pain, reducing the fever, swelling, redness, and tenderness of acute gouty arthritis—see INDICATIONS.

Following single oral doses of Capsules INDOCIN 25 mg or 50 mg, indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 mcg/mL, respectively, at about 2 hours. Orally administered Capsules INDOCIN are virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours. A single 50 mg dose of Oral Suspension INDOCIN was found to be bioequivalent to a 50 mg INDOCIN capsule when each was administered with food.

Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. The mean half-life of indomethacin is estimated to be about 4.5 hours. With a typical therapeutic regimen of 25 or 50 mg t.i.d., the steady-state plasma concentrations of indomethacin are an average 1.4 times those following the first dose.

The rate of absorption is more rapid from the rectal suppository than from Capsules INDOCIN. Ordinarily, therefore, the total amount absorbed from the suppository would be expected to be at least equivalent to the capsule. In controlled clinical trials, however, the amount of indomethacin absorbed was found to be somewhat less (80–90%) than that absorbed from Capsules INDOCIN. This is probably because some subjects did not retain the material from the suppository for the one hour necessary to assure complete absorption. Since the suppository dissolves rather quickly rather than melting slowly, it is seldom recovered in recognizable form if the patient retains the suppository for more than a few minutes.

Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60 percent of an oral dosage is recovered in urine as drug and metabolites (26 percent as indomethacin and its glucuronide); and 33 percent is recovered in feces (1.5 percent as indomethacin). About 99% of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations. Indomethacin has been found to cross the blood-brain barrier and the placenta.

In a gastroscopic study in 45 healthy subjects, the number of gastric mucosal abnormalities was significantly higher in the group receiving Capsules INDOCIN than in the group taking Suppositories INDOCIN or placebo.

In a double-blind comparative clinical study involving 175 patients with rheumatoid arthritis, however, the incidence of upper gastrointestinal adverse effects with Suppositories or Capsules INDOCIN was comparable. The incidence of lower gastrointestinal adverse effects was greater in the suppository group.

INDICATIONS

Indomethacin has been found effective in active stages of the following:

1. Moderate to severe rheumatoid arthritis including acute flares of chronic disease.
2. Moderate to severe ankylosing spondylitis.
3. Moderate to severe osteoarthritis.
4. Acute painful shoulder (bursitis and/or tendinitis).
5. Acute gouty arthritis.

INDOCIN may enable the reduction of steroid dosage in patients receiving steroids for the more severe forms of rheumatoid arthritis. In such instances the steroid dosage should be reduced slowly and the patients followed very closely for any possible adverse effects.

The use of INDOCIN in conjunction with aspirin or other salicylates is not recommended. Controlled clinical studies have shown that the combined use of INDOCIN and aspirin does not produce any greater therapeutic effect than the use of INDOCIN alone. Furthermore, in one of these clinical studies, the incidence of gastrointestinal side effects was significantly increased with combined therapy (see DRUG INTERACTIONS).

CONTRAINDICATIONS

INDOCIN should not be used in:

Patients who are hypersensitive to this product.

Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory agents.

Suppositories INDOCIN are contraindicated in patients with a history of proctitis or recent rectal bleeding.

WARNINGS

General:

Because of the variability of the potential of INDOCIN to cause adverse reactions in the individual patient, the following are strongly recommended:

1. The lowest possible effective dose for the individual patient should be prescribed. Increased dosage tends to increase adverse effects, particularly in doses over 150–200 mg/day, without corresponding increase in clinical benefits.
2. Careful instructions to, and observations of, the individual patient are essential to the prevention of serious adverse reactions. As advancing years appear to increase the possibility of adverse reactions, INDOCIN should be used with greater care in the elderly.
3. Effectiveness of INDOCIN in pediatric patients has not been established. INDOCIN should not be prescribed for pediatric patients 14 years of age and younger unless toxicity or lack of efficacy associated with other drugs warrants the risk.

   In experience with more than 900 pediatric patients reported in the literature or to the manufacturer who were treated with Capsules INDOCIN, side effects in pediatric patients were comparable to those reported in adults. Experience in pediatric patients has been confined to the use of Capsules INDOCIN.

   If a decision is made to use indomethacin for pediatric patients two years of age or older, such patients should be monitored closely and periodic assessment of liver function is recommended. There have been cases of hepatotoxicity reported in pediatric patients with juvenile rheumatoid arthritis, including fatalities. If indomethacin treatment is instituted, a suggested starting dose is 2 mg/kg/day given in divided doses. Maximum daily dosage should not exceed 4 mg/kg/day or 150–200 mg/day, whichever is less. As symptoms subside, the total daily dosage should be reduced to the lowest level required to control symptoms, or the drug should be discontinued.

Gastrointestinal Effects:

Single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestine, have been reported to occur with INDOCIN. Fatalities have been reported in some instances. Rarely, intestinal ulceration has been associated with stenosis and obstruction.

Gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) have occurred. Increased abdominal